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(21) International Application Number: PCT/IB99/01749 (22) International Filing Date: 29 October 1999 (29.10.99) (30) Priority Data: P-9800309 16 December 1998 (16.12.98) SI (71) Applicant (for all designated States except US): LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D. [SI/SI]; Verovskova 57, 1526 Ljubljana (SI). (72) Inventor; and (75) Inventor/Applicant (for US only): KERČ, Jancz [SI/SI]; 1000 Ljubljana (SI).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: STABLE PHARMACEUTICAL FORMULATION COMPRISING A HMG-CoA REDUCTASE INHIBITOR (57) Abstract <p>Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to <i>Aspergillus</i>, <i>Monascus</i>, <i>Nocardia</i>, <i>Amycolatopsis</i>, <i>Mucor</i> or <i>Penicillium</i> genus, and some are obtained by treating the fermentation products using the methods of chemical synthesis or they are the products of total chemical synthesis. The aforementioned active substances may be destabilised by the environmental factors, their degradation may also be accelerated by interactions with other pharmaceutical ingredients, such as fillers, binders, lubricants, glidants and disintegrating agents, therefore the pharmaceutical ingredients and the process for preparation of the pharmaceutical formulation should be meticulously chosen to avoid the aforementioned undesired interactions and reactions. The present invention relates to a stable solid pharmaceutical formulation for the treatment of hypercholesterolemia and hyperlipidemia. More precisely, the present invention relates to the new stable solid pharmaceutical formulation containing as an active ingredient a HMG-CoA reductase inhibitor, such as atorvastatin, pravastatin, fluvastatin and cerivastatin or pharmaceutically acceptable salts thereof.</p>		

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STABLE PHARMACEUTICAL FORMULATION COMPRISING A HMG-CoA REDUCTASE INHIBITOR

Field of the Invention

The present invention relates to a new stable solid
5 pharmaceutical formulation which is particularly suitable
for the treatment of hypercholesterolemia and
hyperlipidemia. More precisely, the present invention
relates to the new stable solid pharmaceutical formulation
containing as an active substance a HMG-CoA reductase
10 inhibitor, such as atorvastatin, pravastatin, fluvastatin
and cervastatin, or pharmaceutically active salts thereof.

Background of the Invention

Lovastatin, pravastatin, simvastatin, mevastatin,
15 atorvastatin, fluvastatin and cervastatin, derivatives and
analogs thereof are known as HMG-CoA reductase inhibitors
and are used as antihypercholesterolemic agents. The
majority of them are produced by fermentation using
microorganisms of different species identified as species
20 belonging to *Aspergillus*, *Monascus*, *Nocardia*, *Amycolatopsis*,
Mucor or *Penicillium* genus. Some are obtained by treating
the fermentation products using the methods of chemical
synthesis like simvastatin or they are the products of total
chemical synthesis like fluvastatin, atorvastatin and
25 cervastatin.

The purity of the active substance is an important
factor for manufacturing a safe and effective pharmaceutical
formulation. Maximum possible purity of the product is of
30 particular importance if the pharmaceutical product must be
taken on a longer term basis in the treatment or prevention
of high cholesterol levels in blood. Accumulation of
impurities from drugs of a lower level of purity may cause a
variety of side effects during treatment. Besides
35 impurities, that cannot be completely eliminated in the
process of preparation of the active substance, degradation

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products occurring by subjecting the final pharmaceutical formulation to various environmental factors such as temperature, moisture, low pH and light, may also impose a problem. HMG-CoA reductase inhibitors occurring in the form of salts in the final pharmaceutical formulation, such as atorvastatin, pravastatin, fluvastatin and cervastatin, are particularly sensitive to an acidic environment in which hydroxy acids are degraded into a lactone.

10 Apart from the fact that the aforementioned active substance may be destabilised by the environmental factors, their degradation may also be accelerated by interactions with other pharmaceutical ingredients, such as fillers, binders, lubricants, glidants and disintegrating agents.

15 Therefore, the pharmaceutical ingredients and the process for preparation of the pharmaceutical formulation should be meticulously chosen to avoid the aforementioned undesired interactions and reactions.

20 The stability of the active substance in an acidic environment is one of the major problems in the case of statins in the form of salts. One of possible solutions of the aforementioned problem is described in EP 0 336 298, disclosing a stable pharmaceutical formulation for

25 pravastatin. The essence of the formulation is to maintain an alkaline environment so that the aqueous dispersion of the pharmaceutical formulation reaches a pH above 9, preferably about 10. In addition to the active substance pravastatin, the composition of the invention includes a

30 basifying agent, such as magnesium oxide which imparts a pH to an aqueous dispersion of the aforementioned formulation above 9. In view of the stability of the active substance such a formulation is effective. However, the

35 local alkaline environment occurring at the site of dissolution of the pharmaceutical formulation may have a negative impact on the gastric mucosa with its normally

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acidic environment. This negative impact may be particularly evident for patients with a damaged gastric mucous membrane where the mucosa per se is not able to create a sufficient acidic environment inside the stomach for normal digestive
5 functioning. It is particularly important in chronic therapies as in the case of prophylaxis or treatment with HMG-CoA reductase inhibitors.

Summary of the Invention

10 It is an object of the present invention to provide a pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor which exerts an excellent stability while avoiding the afore mentioned disadvantages. It is a particular object to provide a stabilized active
15 substance as such where the HMG-CoA reductase inhibitor is precautionary protected from being degraded.

It is a further object to provide a process for the preparation of a stable pharmaceutical formulation which
20 exerts an excellent stability while avoiding the afore mentioned disadvantages.

These and further objects are accomplished by the present invention.

25

According to the present invention, there is provided a stable solid pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor, wherein an active substance is contained which is capable of
30 providing a pH in the range from 7 to 11. Within the meaning of the present invention, the term "active substance" denotes a HMG-CoA reductase inhibitor alone or a mixture thereof with a small amount of a buffering agent. Therefore, the present invention also makes available a stabilized
35 pharmaceutically active substance as such, which active

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substance consists of a HMG-CoA reductase inhibitor and a low amount of a buffering agent.

According to the present invention, there is further
5 provided a stable solid pharmaceutical formulation containing as an active substance a HMG-CoA reductase inhibitor, wherein the pharmaceutical formulation is capable of providing a pH below 9.

10 In addition, according to the present invention, there is provided suitable processes for the preparation of the above specified stable solid pharmaceutical formulation.

According to the present invention, there is further
15 provided a method for the stabilization of a HMG-CoA reductase inhibitor as an active substance in a solid pharmaceutical formulation, wherein an HMG-CoA reductase inhibitor being capable of providing a pH in the range from 7 to 11 is incorporated into a pharmaceutical formulation
20 which is capable of providing a pH below 9.

Brief description of the drawings

Figures 1a is a diagram which shows the growth of weight of a sample of pravastatin in crystal form and a
25 sample of lyophilised pravastatin when exposed to air moisture. Figure 1b shows the corresponding difference in the starting weight and the weight in time.

Figure 2 is a diagram which shows the occurrence of
30 pravastatin in lactone form when pravastatin was dissolved in different buffers with the pH in a range between 7 and 11 (F = phosphate, C = citrate, B = borate).

Figure 3 is a diagram which shows the formation of
35 different degradation products (impurities) when pravastatin

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was dissolved in different buffers with the pH in a range between 7 and 11 (F = phosphate, C = citrate, B = borate).

5 Detailed description of the preferred embodiments

In the inventor's investigations, it was found that there are three major reasons for instability problems in case of a pharmaceutical formulation containing an active substance and in case of a bulk active substance.

10

First, the active substance as such is very hygroscopic and it is impossible to remove all water from it. This is illustrated by the following experiment: 111.07 mg of pravastatin in crystal form (prava izh) and 109.8 mg of lyophilized pravastatin (prava lio) were exposed to air moisture. Their weights were measured in different time intervals. The growth of weight of both samples and the difference in the starting weight and the weight in time are illustrated in Figures 1a and 1b.

20

Another observation was that carbon dioxide from the air can irreversibly bind to the active substance and can cause a drop of pH. This is illustrated by the following experiment: 5 g of pravastatin sodium were dissolved in 30 ml of methanol, the pH was adjusted to 10 with 3% aqueous solution of NaOH. 400 ml of ethylacetate were added and the crystals of pravastatin sodium were formed. Crystals were filtered and dried and then put into three different atmospheres: normal air, nitrogen atmosphere and carbon dioxide atmosphere. In normal air and in the nitrogen atmosphere the pH remained the same during a period of 24 hours (normal air: 9.2, nitrogen: 9.5), but in the carbon dioxide atmosphere the pH dropped in the first two minutes from 9.2 to 6.9. After 12 minutes the pH was 6.6 and after 1 hour the pH was 6.5. After that, the pH remained constant.

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The third observation is that a sufficient stabilization of the active substance is already obtained at a pH of at least 7.0, but a beneficially high stability is effected at a pH of at least 8.0. We have noticed that at a pH below 8 the formation of lactone has occurred and also the amount of other impurities has increased. The presence of humidity in the air and a carbon dioxide-rich atmosphere makes the negative effect of a low pH even stronger. This is illustrated by the following experiment: Pravastatin was dissolved in different buffers with the pH in a range between 7 and 11 (F = phosphate, C = citrate, B = borate). The occurrence of pravastatin in lactone form and the formation of different degradation products (impurities) was measured after 1, 5, 13 and 28 days. The results are shown in Figures 2 and 3.

In the present invention, we have surprisingly found that a sufficient stability of the active substance, which is a HMG-CoA reductase inhibitor preferably in the form of salt, can be also obtained by using a pharmaceutical formulation which does not create a marked alkaline environment in an aqueous dispersion.

Further, we have found that for the stability and digestibility of a pharmaceutical formulation both the pH generated by the formulation in an aqueous medium (usually being a dispersion) and the pH of the active substance (HMG-CoA reductase inhibitor) are of great importance.

Another surprising finding was that a sufficient stability of a HMG-CoA reductase inhibitor in the form of a salt in bulk can be obtained by the addition of small amounts of a buffering agent to the pure HMG-CoA reductase inhibitor in the form of salt. Such an addition of small amounts of buffering agents avoids the negative effect of water already present in the bulk substance and of moisture.

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from the air, to avoid the negative effect of low pH caused by other ingredients which will be co-admixed to the pharmaceutical formulation, and to avoid the possible lowering of the pH caused by carbon dioxide.

5

The active substance and the pharmaceutical formulation according to the present invention were designed to avoid the negative effect of the water present in the bulk substance and in the pharmaceutical formulation, to avoid
10 the negative effect of low pH which can be caused by other ingredients of the pharmaceutical formulation and to avoid possible lowering of the pH caused by carbon dioxide.

The most acceptable stability of the active substance
15 in the formulations is obtained with an active substance which is capable of providing a pH in the range from 7 to 11. The pH value is the one which is obtained when the pH of an aqueous medium containing said active substance would be measured. In the stable pharmaceutical formulation according
20 to the present invention, the basic pH of the active substance has a minimal influence on the pH of the formulation which is lower than 9. By creating locally an environment around the active substance which affords the best stability for the active substance, the potential of
25 negative impact of other ingredients of the composition of the pharmaceutical formulation is reduced, and possible reactions among the active substance and the rest of the ingredients of the composition of the pharmaceutical formulation are also less favoured. Accordingly, the active
30 substance is maintained in a stable form when an active substance which is capable of providing a pH in an aqueous medium in the range from 7 to 11 is added to the pharmaceutical formulation.

35 The active substance being added to the formulation of the present invention generally is a HMG-CoA reductase

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inhibitor in the form of a salt. The pH of the active substance may be adjusted within the above specified range in the course of preparing the salt of the HMG-CoA reductase inhibitor from the acid form and an alkaline substance. As

5 an example, the preparation of pravastatin sodium from pravastatin acid and sodium hydroxide may be mentioned. For a preferred adjustment of the pH of the active substance to be incorporated into the formulation within the above specified range of 7 to 11, the active substance is further

10 mixed with an appropriate buffering agent. Accordingly, the active substance may contain small amounts of a buffering agent, preferably less than 1%, more preferably 0.1 to 0.5%, most preferably approximately 0.3%, based on the weight of the active substance added to the formulation. A suitable

15 buffering agent for this purpose is carbonate buffer or phosphate buffer, such as sodium carbonate or sodium phosphate. For example, an amount 0.3% of sodium carbonate in pravastatin results in a pH of pravastatin between 9 and 10. Thus, it is possible to mix pravastatin with other

20 ingredients of the pharmaceutical formulation without fear that a degradation can be caused by the contact of pravastatin with acidic ingredients as a microenvironment of pravastatin is still basic due to the addition of small amounts of a buffering agent. This addition of small amounts

25 of a buffering agent is also important for an easier handling of the pravastatin bulk without special requirements for a carbon dioxide free atmosphere. Preferably, the acidifying effect of carbon dioxide on the final formulation is neutralised by further addition of an

30 appropriate buffering agent to adjust the pH of the formulation in the above specified range, preferably by addition of 20%, more preferably of 10% per weight based on the total weight of the tablet. Any buffering agent capable of adjusting the pH of the total formulation in the desired

35 range is suitable, including sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium

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carbonate, hydrogen phosphate, phosphate, sulphate, sodium
or magnesium carbonate, sodium ascorbate, benzoate, sodium
or potassium hydrogen carbonate, lauryl sulphate, or
mixtures of such buffering agents. Citrate buffer, carbonate
5 buffer and phosphate or hydrogen phosphate buffer may be
mentioned as specific examples.

Preferably, an active substance contained in the
pharmaceutical formulation according to the present
10 invention is capable of providing a pH in the range from 8
to 10.

Furthermore, the active substance may be selected from
the group consisting of pravastatin, atorvastatin,
15 fluvastatin, cerivastatin and a pharmaceutically acceptable
salt thereof. Preferably, the active substance is a sodium
salt of pravastatin (pravastatin Na) or a calcium salt of
atorvastatin (atorvastatin Ca).

20 As mentioned above, it is a further significant aspect
of the present invention that the pharmaceutical formulation
is capable of providing a pH below 9, preferably below 8.5.
The lower limit of the pH generated by the pharmaceutical
formulation suitably is 6, preferably 7.

25 By following the concepts of the present invention, the
solid pharmaceutical formulation is stable such that the
HMG-CoA reductase inhibitor as the active substance does not
tend to be decomposed and essentially retains its activity.
30 Thereby, it is ensured that the active substance in the
pharmaceutical formulation according to the present
invention shows a sufficient stability while, at the same
time, avoiding the negative impact of a high local alkaline
environment at the site of dissolution of the pharmaceutical
35 formulation on the gastric mucosa which would occur if the
pH of an aqueous dispersion of the pharmaceutical

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formulation is 9 or more and which results in anormal digestive functioning.

The pharmaceutical formulation of this invention may include, in addition to the HMG-CoA reductase inhibitor which is sensitive to a low pH environment, one or more fillers, such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextrin, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulphate, one or more binders, such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxymethyl cellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminium silicate, one or more disintegrating agents such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminium silicate, polyacrylin potassium, one or more different glidants such as magnesium stearate, calcium stearate, zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering agents such as sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulphate, sodium or magnesium carbonate, sodium ascorbate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents.

If required any, the formulation may also include surfactants and other conventional components for solid, pharmaceutical formulations such as colouring agents, lakes, aromas and adsorbents. As surfactants the following may be

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used: ionic surfactants, such as sodium lauryl sulphate or non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitan and fatty acids (such as Span®, manufactured by Atlas Chemie), esters of polyoxyethylenesorbitan and fatty acids (such as Tween®, manufactured by Atlas Chemie), polyoxyethylated hydrogenated castor oil (such as Cremophor®, manufactured by BASF), polyoxyethylene stearates (such as Brij®, manufactured by Atlas Chemie), dimethylpolysiloxane or any combination of the above mentioned surfactants.

If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, at least from one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.

20

The solid pharmaceutical formulations according to the present invention may be prepared as described below:

• The mixture of the active substance, filler, binder, buffering agent, disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenised employing suitable mixers. Glidants and/or lubricants are added and the mixture is re-homogenised. The resulting mixture is compressed into tablets or filled into capsules. If needed, tablets can be film-coated.

• The mixture of the active substance, filler, binder, buffering agent, disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenised employing

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suitable mixers, granulated with a suitable solvent such as water, ethanol, methanol, isopropyl alcohol, n-butyl alcohol, acetone, diethyl ether, ethyl acetate, isopropyl acetate, methyl acetate, dichloromethane and methanol, and mixtures of these solvents such as ethanol and acetone, methanol and acetone, dichloromethane and methanol, and the mixtures thereof. The resulting granulation is dried in suitable dryers such as standard plate dryers, fluid bed dryers, vacuum and microwave dryers. To the dried granulation, glidants and/or lubricants and if required other conventional ingredients for solid pharmaceutical formulations are added. The resulting mixture is rehomogenised and compressed into tablets or filled into capsules. Optionally, tablets are film-coated.

15

Moreover, according to the present invention the HMG-CoA reductase inhibitor as an active substance in a solid pharmaceutical formulation can be effectively stabilized by incorporating a HMG-CoA reductase inhibitor, which is capable of providing a pH in the range from 7 to 11, into a pharmaceutical formulation which is capable of providing a pH below 9. The pH generated by the pharmaceutical formulation may be adjusted by the incorporation of appropriate agents such as buffering agents and the like.

20
25

The present invention is illustrated but by no means limited by the following examples.

30 **EXAMPLES**

Example 1

The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the hereinunder listed ingredients were homogenised and the resulting mixture was then compressed

35

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into tablets each containing 5, 10, 20 or 40 mg of pravastatin sodium.

The pH of the aqueous dispersion of this formulation is 8.3.

5

Ingredients	% by weight
Pravastatin sodium (pH 8.2)	5%
Lactose	37.5%
Microcrystalline cellulose	38%
Sodium citrate	10%
Magnesium aluminium silicate	2%
Polyacrylin potassium	3%
Talc	3%
Silicon dioxide	0.5%
Magnesium stearate	1%

Example 2

The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the hereinunder listed ingredients were homogenised and the resulting mixture was then compressed into tablets each containing 5, 10, 20, 40 or 80 mg of pravastatin sodium.

The pH of the aqueous dispersion of this formulation is 8.0.

Ingredients	% by weight
Pravastatin sodium (pH 8.5)	10%
Lactose	32%
Microcrystalline cellulose	37%
Sodium citrate	10%
Croscarmellose sodium	2%
Sodium lauryl sulphate	0.5%
Polyacrylin potassium	3%

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Talc	3%
Silicon dioxide	0.5%
Calcium stearate	2%

Example 3

The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows: the first six hereinunder listed ingredients were homogenised, granulated with water, dried, the remainder of the below listed ingredients were added and homogenised and the resulting mixture was then compressed into tablets each containing 5, 10, 20 or 40 mg of pravastatin sodium.

The pH of the aqueous dispersion of this formulation is 8.2.

Ingredients	% by weight
Pravastatin sodium (pH 9)	5%
Lactose	20%
Microcrystalline cellulose	20%
Hydroxypropyl cellulose	1.5%
Sodium citrate	10%
Magnesium aluminium silicate	2%
Polyacrylin potassium	3%
Microcrystalline cellulose	35%
Talc	3%
Magnesium stearate	0.5%

15

Example 4

The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as follows (ingredients are listed in the following table): the mixture of the active substance, filler, buffering agent, disintegrant and surfactant is homogenised employing suitable mixers. Glidants and lubricants are added

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and the mixture is re-homogenised. The resulting mixture is compressed into tablets. The pH of the aqueous dispersion of this formulation is 8.5.

Ingredient	% by weight	function
pravastatin sodium*	8.3	active substance
lactose	58.3	filler
microcrystalline cellulose	14.4	filler
Na ₂ HPO ₄	10	buffering agent
Na lauryl sulphate	0.4	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	4	disintegrant
colloidal silicon dioxide	0.5	glidant
talc	3	glidant, lubricant
magnesium stearate	1	lubricant

- 5 * pravastatin contains 0.3% of Na₂CO₃, so that the pH of the active substance is between 9 and 10. The percentage in the above mentioned formulation is calculated for the tablets containing 40 mg of pravastatin. The amount of pravastatin can be 80, 40, 20, 10 or 5 mg.

10

Example 5

- The pharmaceutical formulation with the active ingredient pravastatin sodium in the form of tablets was prepared as in Example 4. The resulting mixture is compressed into tablets. The pH of the aqueous dispersion of this formulation is 8.3.

Ingredient	% by weight	function
pravastatin sodium*	8.3	active substance
lactose	58.3	filler
microcrystalline cellulose	16.5	filler

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Na ₂ HPO ₄ (dried)	7.9	buffering agent
sodium lauryl sulphate	0.4	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	4	disintegrant
colloidal silicon dioxide	0.5	glidant
talc	3	glidant, lubricant
magnesium stearate	1	lubricant

* pravastatin contains 0.3% of Na₂CO₃, so that the pH of the active substance is between 9 and 10. The amount of pravastatin can be 80, 40, 20, 10 or 5 mg.

5 Example 6

The pharmaceutical formulation with the active ingredient atorvastatin calcium in the form of tablets was prepared as in Example 4. The resulting mixture is compressed into tablets.

10

Ingredient	weight (mg)	function
Atorvastatin calcium	20.0	active substance
lactose	140.0	filler
microcrystalline cellulose	34.8	filler
Na ₂ HPO ₄ (dried)	24.0	buffering agent
Na lauryl sulphate	2.0	absorption accelerator, surfactant
cross-linked carboxymethylcellulose	9.6	disintegrant
colloidal silicon dioxide	1.2	glidant
talc	7.2	glidant, lubricant
magnesium stearate	1.2	lubricant

In case of higher or lower dosages of atorvastatin calcium (80, 40, 10 or 5 mg), proportional higher or smaller amounts

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of other ingredients are used, or proportional bigger or smaller tablets are prepared.

- 5 Tablets containing pravastatin or atorvastatin which were formed according to Examples 1 to 6 were subjected to stability studies and it was found that the tablets provide an excellent stability; essentially no degradation products of pravastatin or atorvastatin were observed.

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Claims

1. A stable solid pharmaceutical formulation containing as
an active substance a HMG-CoA reductase inhibitor,
5 characterized in that
an active substance is contained which is capable of
providing a pH in the range from 7 to 11.
2. A stable solid pharmaceutical formulation as defined in
10 Claim 1,
characterized in that
an active substance is contained which is capable of
providing a pH in the range from 8 to 10.
- 15 3. A stable solid pharmaceutical formulation as defined in
Claim 1 or 2, wherein the active substance is a HMG-CoA
reductase inhibitor in the form of a salt.
4. A stable solid pharmaceutical formulation as defined in
20 any one of claims 1 to 3, wherein the active substance,
which had been incorporated into the formulation, contained
a buffering agent.
5. A stable solid pharmaceutical formulation as defined in
25 Claim 4, wherein the active substance, which had been
incorporated into the formulation, contained the buffering
agent in an amount of less than 1%.
6. A stable solid pharmaceutical formulation as defined in
30 any one of claims 1 to 5, wherein the active substance is
selected from the group consisting of pravastatin,
atorvastatin, fluvastatin, cerivastatin and a
pharmaceutically acceptable salt thereof.
- 35 7. A stable solid pharmaceutical formulation as defined in
Claim 6, wherein the active substance is a sodium salt of

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pravastatin (pravastatin Na) or a calcium salt of atorvastatin (atorvastatin Ca).

8. A stable solid pharmaceutical formulation as defined in
5 Claim 1, which further comprises at least one constituent
selected from the group consisting of a filler, a binder, a
disintegrating agent, a glidant, a buffering agent;
optionally further comprising at least one constituent
selected among colouring agents, lakes, aromas, adsorbents,
10 film formers and plasticizers.
9. A stable solid pharmaceutical formulation containing as
an active substance a HMG-CoA reductase inhibitor,
characterized in that
15 the pharmaceutical formulation is capable of providing a pH
below 9.
10. A stable solid pharmaceutical formulation according to
claim 9,
20 characterized in that
the pharmaceutical formulation is capable of providing a pH
in the range from 6 to 9.
11. A stable solid pharmaceutical formulation according to
25 claim 9,
characterized in that
the pharmaceutical formulation is capable of providing a pH
in the range from 7 to 8.5.
- 30 12. A stable solid pharmaceutical formulation according to
claim 9,
characterized in that
an active substance being capable of providing a pH in the
range from 7 to 11 is incorporated into said solid
35 pharmaceutical formulation.

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13. A stable solid pharmaceutical formulation according to claim 9, characterized in that an active substance being capable of providing a pH in the range from 8 to 10 is incorporated into said solid pharmaceutical formulation.
14. A stable solid pharmaceutical formulation as defined in Claim 12 or 13, wherein the active substance is a HMG-CoA reductase inhibitor in the form of a salt.
15. A stable solid pharmaceutical formulation according to any one of claims 12 to 14, wherein the incorporated active substance contains a buffering agent.
16. A stable solid pharmaceutical formulation according to claim 15, wherein the buffering agent is contained in an amount of less than 1%.
17. A stable solid pharmaceutical formulation according to claim 15, wherein additional amounts of a buffering agent are incorporated into said formulation.
18. A stable solid pharmaceutical formulation according to any one of claims 9 to 17, wherein the active substance is selected from the group consisting of pravastatin, atorvastatin, fluvastatin, cerivastatin and a pharmaceutically acceptable salt thereof.
19. A stable solid pharmaceutical formulation as defined in Claim 18, wherein the active substance is a sodium salt of pravastatin (pravastatin Na) or a calcium salt of atorvastatin (atorvastatin Ca).
20. A stable solid pharmaceutical formulation as defined in Claim 9, which further comprises at least one constituent

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selected from the group consisting of a filler, a binder, a disintegrating agent, a glidant, a buffering agent; optionally further comprising at least one constituent selected among colouring agents, lakes, aromas, adsorbents, film formers and plasticizers.

21. A process for the preparation of a stable solid pharmaceutical formulation according to any of the aforementioned claims, wherein the mixture of the active substance, filler, binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations are homogenised in suitable mixers, glidants and/or lubricants are added, the mixture is then re-homogenised and the resulting mixture is compressed into tablets or filled into capsules; optionally the tablets may be film-coated.

22. A process for the preparation of a stable solid pharmaceutical formulation according to any of the claims 1 to 20, wherein the mixture of the active substance, filler, binder, buffering agent, disintegrating agent and optionally surfactant and other commonly used ingredients for solid pharmaceutical formulations are homogenised in suitable mixers, granulated with a suitable solvent; the resulting granulation is dried in suitable dryers; to the dried granulations, glidants and/or lubricants are added and optionally other ingredients for solid pharmaceutical formulations and the resulting mixture is re-homogenised and compressed into tablets or filled into capsules; optionally the tablets may be film-coated.

23. A stabilized pharmaceutically active substance consisting only of a mixture of a HMG-CoA reductase inhibitor and a buffering agent.

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24. A stabilized pharmaceutically active substance according to claim 23, wherein the buffering agent is present in the mixture in an amount of less than 1 wt.-% based on the total weight of the pharmaceutically active substance.

25. A stabilized pharmaceutically active substance according to claim 23 or 24, wherein the HMG-CoA reductase inhibitor is in the form of a salt.

26. A stabilized pharmaceutically active substance according to claim 23 or 24, wherein the buffering agent imparts a pH in the range from 7 to 11 to the pharmaceutically active substance.

27. A stabilized pharmaceutically active substance according to any one of claims 23 to 26, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin, atorvastatin, fluvastatin, cerivastatin and a pharmaceutically acceptable salt thereof.

28. A stabilized pharmaceutically active substance according to claim 27, wherein the HMG-CoA reductase inhibitor is a sodium salt of pravastatin (pravastatin Na) or a calcium salt of atorvastatin (atorvastatin Ca).

29. A method for the stabilization of a HMG-CoA reductase inhibitor as an active substance in a solid pharmaceutical formulation, wherein an active substance being capable of providing a pH in the range from 7 to 11 is incorporated into a pharmaceutical formulation which is capable of providing a pH below 9.

30. The method according to claim 29, wherein the pharmaceutical formulation is capable of providing a pH in the range from 6 to 9.

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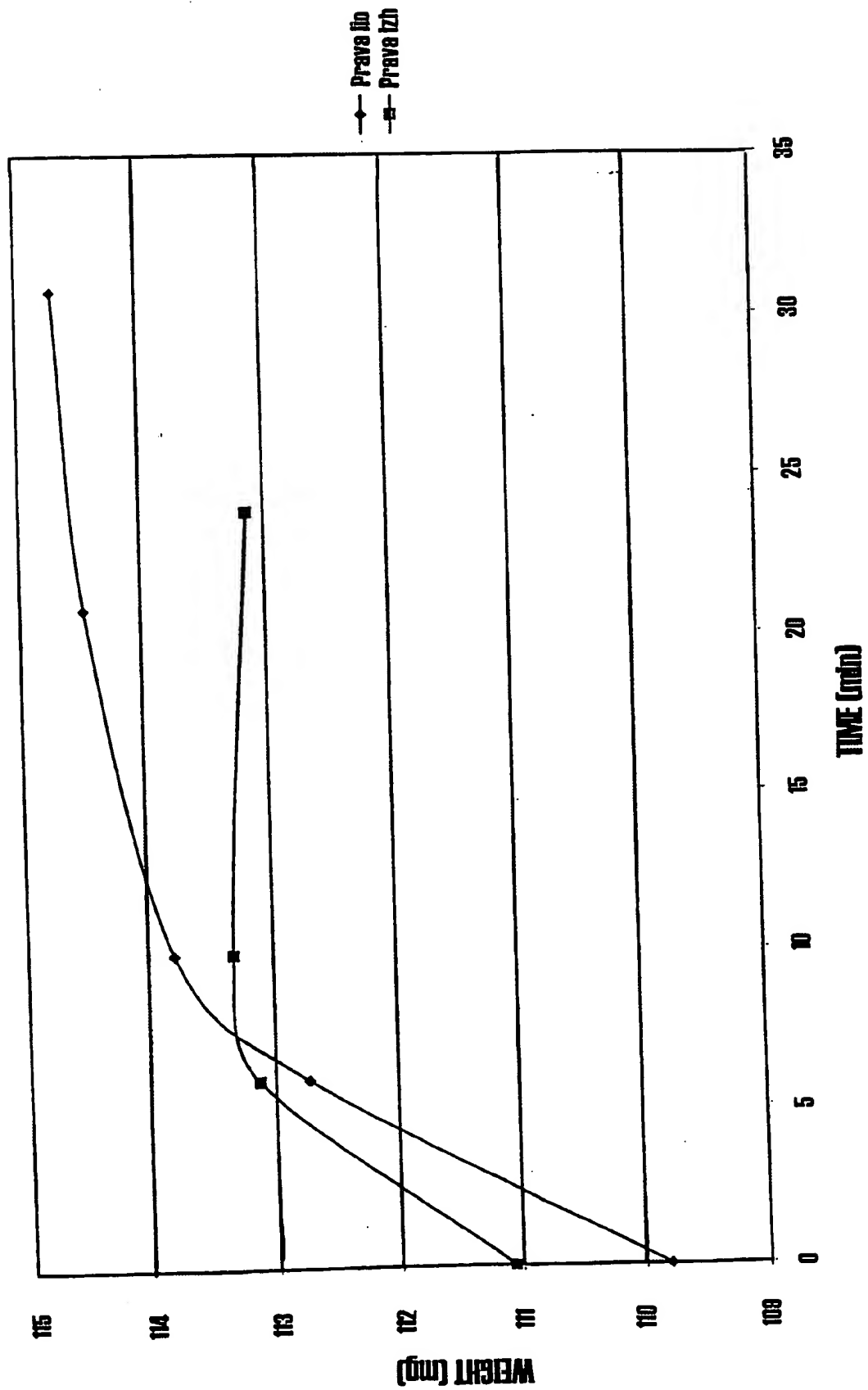
31. The method according to claim 29, wherein the pharmaceutical formulation is capable of providing a pH in the range from 7 to 8.5.
- 5 32. The method according to claim 29, wherein the active substance is a HMG-CoA reductase inhibitor in the form of a salt.
- 10 33. The method according to claim 29, wherein the incorporated active substance contains a buffering agent in order to provide a pH for said active substance in the range from 7 to 11.
- 15 34. The method according to claim 33, wherein the incorporated active substance contains less than 1% of a buffering agent.
- 20 35. The method according to claim 33 or 34, wherein additional amounts of a buffering agent are incorporated into the pharmaceutical formulation in order to provide a pH for said pharmaceutical formulation of below 9.
- 25 36. The method according to any one of claims 29 to 35, wherein the active substance is selected from the group consisting of pravastatin, atorvastatin, fluvastatin, cerivastatin and a pharmaceutically acceptable salt thereof.
- 30 37. The method according to claim 36, wherein the active substance is a sodium salt of pravastatin (pravastatin Na) or a calcium salt of atorvastatin (atorvastatin Ca).
- 35 38. The method according to claim 29, wherein said stable solid pharmaceutical formulation further comprises at least one constituent selected from the group consisting of a filler, a binder, a disintegrating agent, a glidant, a

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buffering agent; optionally further comprising at least one constituent selected among colouring agents, lakes, aromas, adsorbents, film formers and plasticizers.

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FIGURE 1 A



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FIGURE 1B

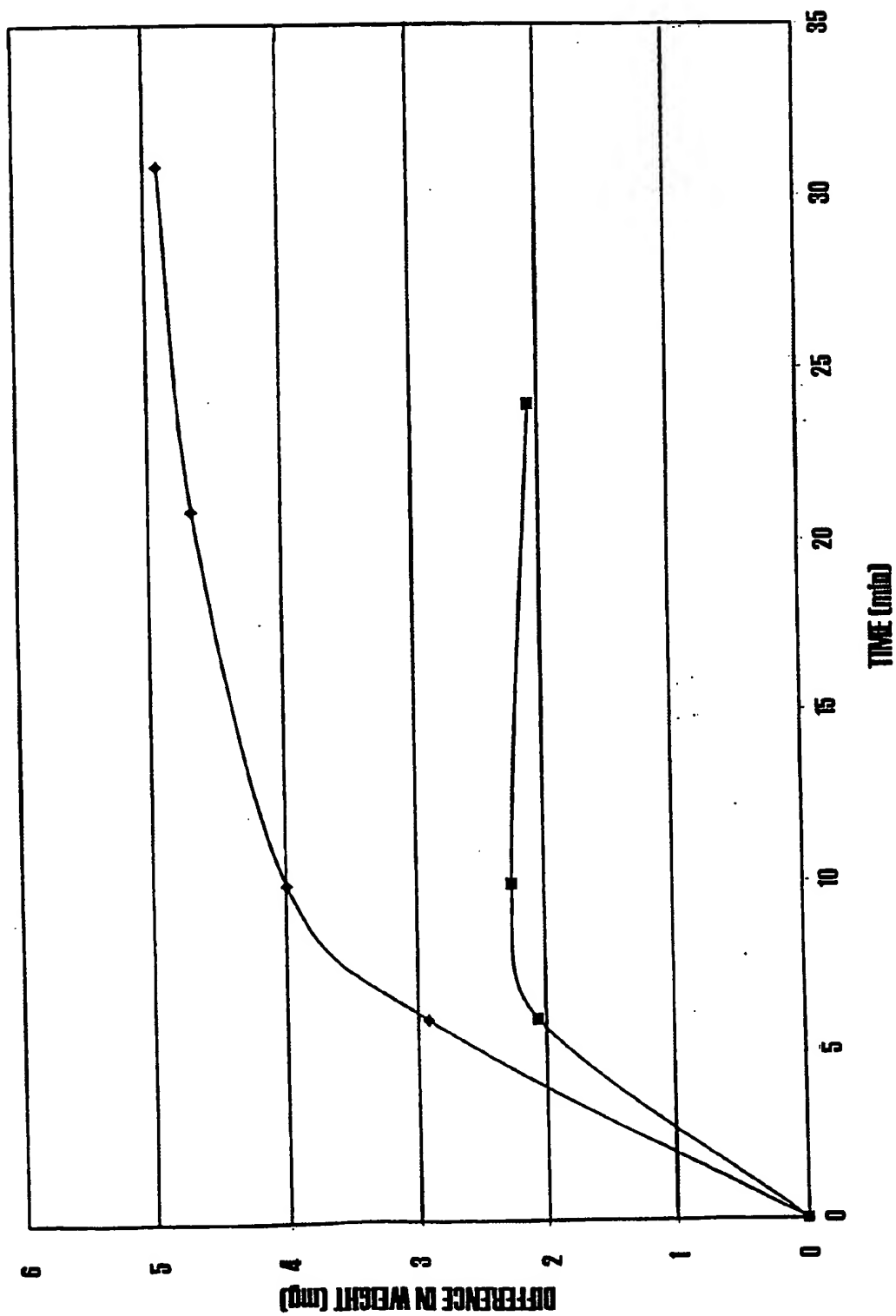
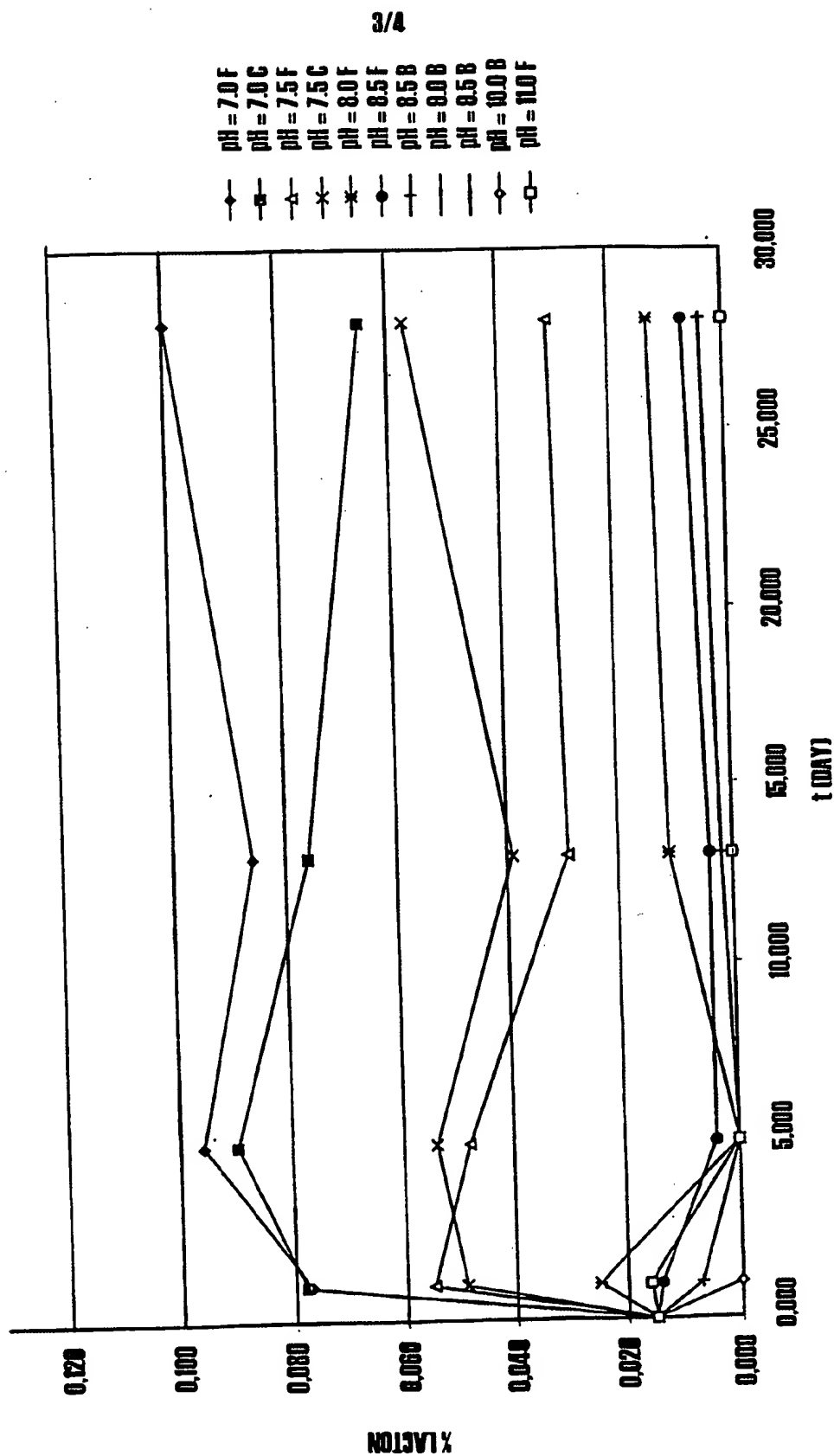
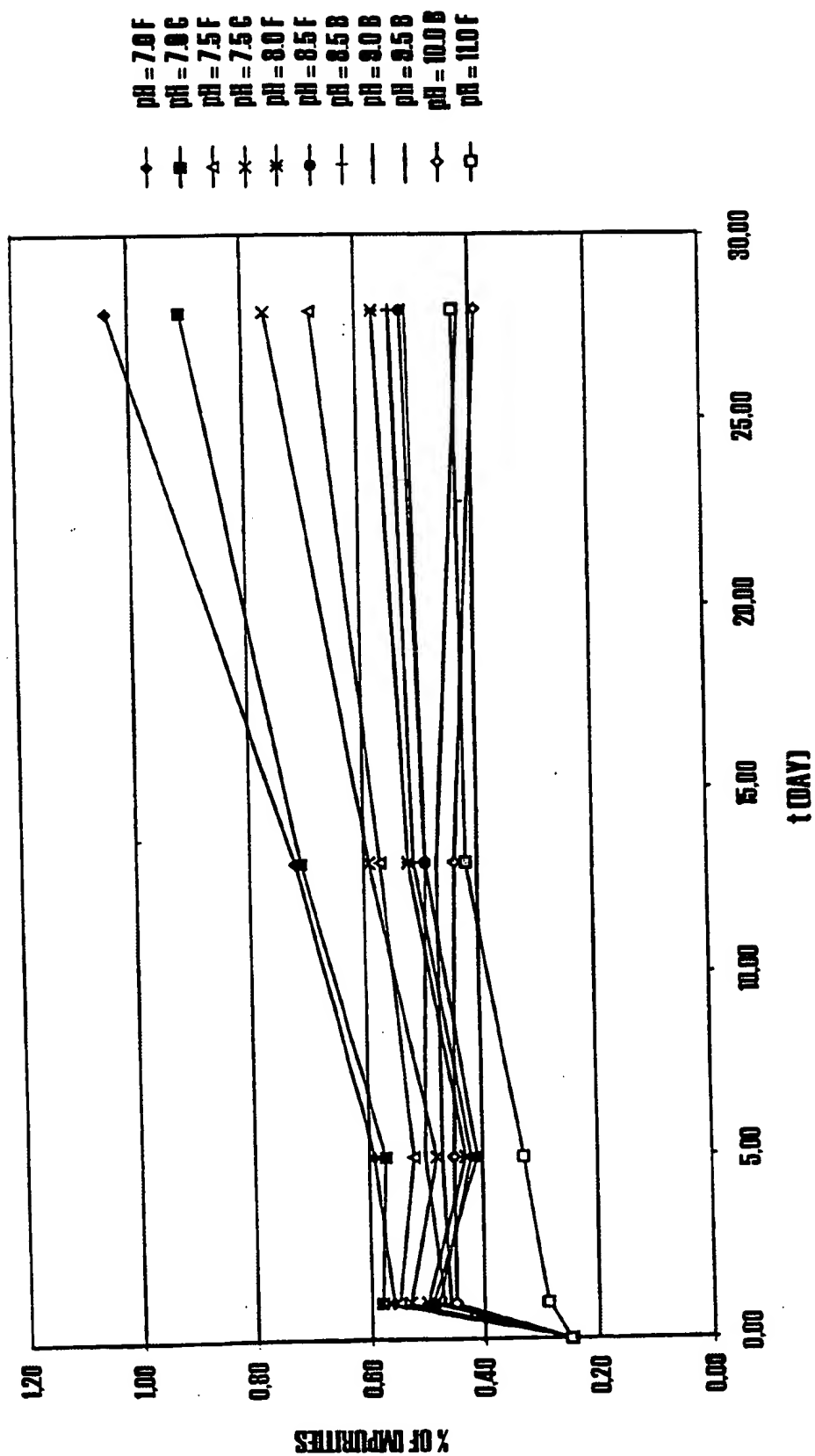


Figure 2 PRAVASTATIN, AT DIFFERENT pH, LACTON



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Figure 3 PRAVASTATIN, AT DIFFERENT pH, IMPURITIES



INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01749

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22 A61K31/22 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 798 375 A (HORIKOSHI HIROYOSHI ET AL) 25 August 1998 (1998-08-25) column 20; example 1	1-22, 29-38
X	EP 0 547 000 A (SANDOZ LTD) 16 June 1993 (1993-06-16) page 3, line 35 - line 48 page 4, line 3 - line 14 page 8 -page 9; example 1 claim 10 ----- -/-	1-6, 8-18, 20-27, 29-36, 38

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

19 May 2000

Date of mailing of the international search report

25/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01749

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 23200 A (KOWA CO ;NISSAN CHEMICAL IND LTD (JP); MURAMATSU TOYOJIRO (JP); MA) 3 July 1997 (1997-07-03)</p> <p>page 3, line 21 -page 4, line 8 page 5, line 3 - line 18 page 7, line 20 -page 8, line 2 page 10 -page 11; examples 2-4</p>	<p>1-5, 8-17, 20-22, 29-35,38</p>
X	<p>EP 0 336 298 A (SQUIBB & SONS INC) 11 October 1989 (1989-10-11) cited in the application</p> <p>page 3 -page 4; example 1 page 2, line 6 - line 43</p>	<p>1,2,4-6, 8-10,12, 13, 15-18, 29,30, 33-36,38</p>
X	<p>WO 94 16693 A (WARNER LAMBERT CO) 4 August 1994 (1994-08-04) , sentence 8 - sentence 21 page 15, line 18 - line 33</p>	<p>21-25, 27,28</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01749

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 9, 23, 29
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 99 01749

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,9,23,29

Present claims 1,9,23 and 29 relate to compounds defined by reference to a desirable pharmacological activity, namely "Hmg-CoA reductase inhibitors".

However, a compound cannot be sufficiently characterised by its pharmacological profile or its mode of action as it is done by an expression like "HMG-CoA reductase inhibitor" because it is impossible to know which substances are encompassed in this expression. Moreover, the problem of the present application, namely the stabilization of these compounds cannot be related with their pharmacological profile, but rather with their common chemical structure.

The claims cover all compounds having this activity, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the concept of "Hmg-CoA reductase inhibitors", to the compounds of claim 6,18, 27, 36, and their salts, and the compounds disclosed in a list in the description of the present application, on page 1, lines 4-15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IB 99/01749

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5798375	A	25-08-1998	AU 706628 B	17-06-1999
			AU 5626196 A	16-01-1997
			CA 2180296 A	04-01-1997
			CN 1148492 A	30-04-1997
			CZ 9601982 A	15-01-1997
			EP 0753298 A	15-01-1997
			HU 9601808 A	28-04-1997
			IL 118778 A	14-07-1999
			JP 9071540 A	18-03-1997
			NO 962784 A	06-01-1997
			NZ 286920 A	24-06-1997
EP 0547000	A	16-06-1993	AT 401872 B	27-12-1996
			AT 190595 A	15-05-1996
			AT 401870 B	27-12-1996
			AT 244992 A	15-05-1996
			AU 661075 B	13-07-1995
			AU 3006992 A	17-06-1993
			CA 2085037 A	13-06-1993
			CH 684309 A	31-08-1994
			CZ 9203633 A	15-09-1993
			CY 1994 A	05-09-1997
			DE 4240430 A	17-06-1993
			FI 925615 A	13-06-1993
			FR 2684876 A	18-06-1993
			GB 2262229 A, B	16-06-1993
			HK 25597 A	06-03-1997
			HU 63328 A	30-08-1993
			IL 104041 A	27-12-1998
			IT 1256698 B	12-12-1995
			JP 2774037 B	09-07-1998
			JP 5246844 A	24-09-1993
			LU 88201 A	09-09-1994
			MX 9207152 A	01-07-1993
			NO 302099 B	26-01-1998
			NZ 245421 A	27-11-1995
			NZ 270729 A	27-11-1995
			RO 111542 A	29-11-1996
			SK 363392 A	09-11-1994
			US 5356896 A	18-10-1994
			ZA 9209642 A	13-06-1994
WO 9723200	A	03-07-1997	AU 1171597 A	17-07-1997
			CA 2213608 A	03-07-1997
			CZ 9702681 A	13-05-1998
			EP 0814782 A	07-01-1998
			JP 11503763 T	30-03-1999
			NO 973814 A	13-10-1997
			NZ 324446 A	30-08-1999
			PL 321868 A	22-12-1997
			SK 116097 A	04-03-1998
EP 0336298	A	11-10-1989	US 5030447 A	09-07-1991
			AT 79030 T	15-08-1992
			AU 3027689 A	05-10-1989
			CA 1323836 A	02-11-1993
			CN 1036508 A, B	25-10-1989
			CY 1675 A	10-10-1993

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/IB 99/01749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0336298 A		DE 68902344 D	10-09-1992
		DE 68902344 T	07-01-1993
		DK 155689 A	01-10-1989
		HK 40093 A	30-04-1993
		IE 62956 B	08-03-1995
		JP 2006406 A	10-01-1990
		JP 2935220 B	16-08-1999
		NZ 228076 A	26-04-1991
		SG 107292 G	24-12-1992
		US 5180589 A	19-01-1993
		ZA 8901424 A	25-10-1989
WO 9416693 A	04-08-1994	AT 178794 T	15-04-1999
		CA 2150372 A	04-08-1994
		DE 69324504 D	20-05-1999
		DE 69324504 T	26-08-1999
		EP 0680320 A	08-11-1995
		ES 2133158 T	01-09-1999
		GR 3030359 T	30-09-1999
		JP 8505640 T	18-06-1996
		MX 9400281 A	29-07-1994
		SG 45369 A	16-10-1998
		US 5686104 A	11-11-1997